European Medicines Agency
*Evaluation of Medicines for Human Use*

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**ASSESSMENT REPORT**
**FOR**
**ANGIOX**

**International non-proprietary name/Common name:**
**bivalirudin**

**Procedure No. EMEA/H/C/II/0024**

**Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**



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# I. SCIENTIFIC DISCUSSION

## 1.1. Introduction

Bivalirudin (Angiox) is an intravenous, anticoagulant that acts via reversible, bivalent direct thrombin inhibition. It is a short, chemically synthesised peptide of 20 amino acids that binds to both the active site and substrate recognition exosite of thrombin, directly and specifically inhibiting all known actions of thrombin. This includes inhibition of protease actions such as conversion of fibrinogen to fibrin and direct cellular signalling actions such as activation of platelets.

Angiox was authorised in September 2004. The following indications are currently approved:

> *For the treatment of adult patients with acute coronary syndromes (unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI)) planned for urgent or early intervention. Angiox should be administered with aspirin and clopidogrel.*
>
> *An anticoagulant in patients undergoing percutaneous coronary intervention (PCI).*

This Type II variation for Angiox concerns a new indication to include the use of bivalirudin in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention. The MAH has applied for the following extension of indication:

> *"Angiox is indicated for patients undergoing percutaneous coronary intervention (PCI),* ***including patients with ST elevation myocardial infarction (STEMI) undergoing primary PCI****".*

## 1.2 Clinical aspects

The primary PCI STEMI clinical development program includes two new studies:

1.- pilot safety study (BIAMI, TMC-BIV-04-01) conducted between 12th April 2004 and 2nd December 2005.

2.- pivotal study– the Harmonizing Outcomes with RevascularIZatiON and Stents (HORIZONS) study (G040188) conducted between 25th March 2005 and 3rd August 2007.

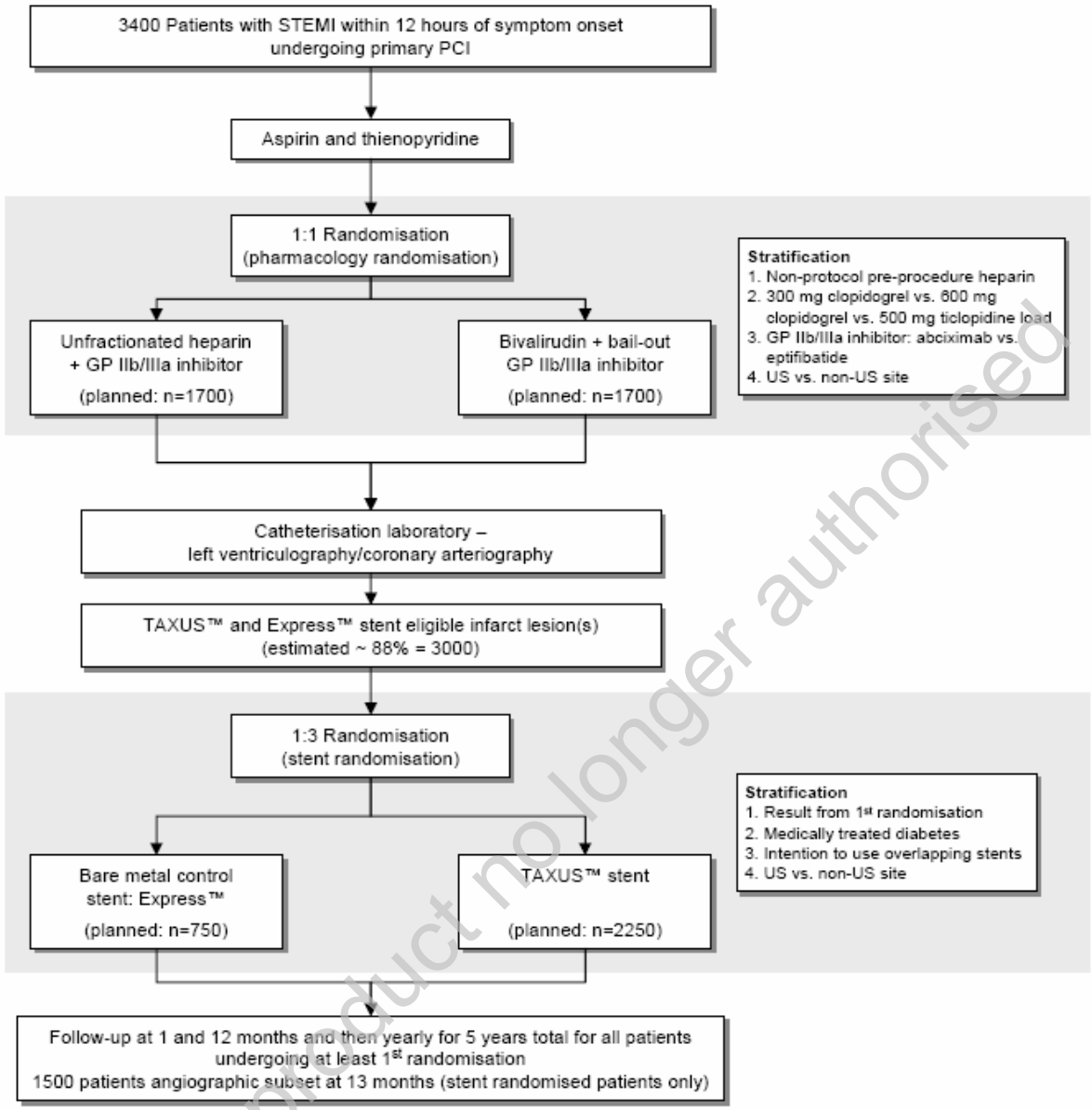
- **HORIZONS AMI Study (G040188)**

*Study Design*

This study was designed as a multicenter, multinational, prospective, randomised, single-blind, active-controlled, parallel-arm to establish the safety and efficacy of the use of bivalirudin in patients with STEMI undergoing a primary PCI strategy. The study was performed at 123 study centres in 11 countries (Austria, Germany, Italy, Norway, Poland, Spain, The Netherlands, and The United Kingdom (UK) in Europe, as well as Argentina, Israel, and the US).

There were 2 components of the study, a pharmacology randomisation (primary randomisation; 30-day analysis) and a stent randomisation (secondary randomisation; 1-year analysis). Following angiography, patients with lesions eligible for stenting were to undergo a second randomization (3:1) to stent implantation with either a slow rate-release paclitaxel-eluting stent (TAXUS™) or an otherwise identical uncoated bare metal stent (EXPRESS™). The 30-day results of the pharmacology randomisation were reported pooled across the stent randomisation. The data provided by the Applicant focuses on the data from the 30-days analysis.

**Figure 1 Study Design of the HORIZONS AMI Study**






*Methods*

Main Inclusion Criteria

Patients were required to fulfil all of the following criteria:

1. Patients had to be at least 18 years of age (there was no upper age limit).

2. Patients had to have clinical symptoms consistent with AMI (e.g. angina or anginal equivalent) lasting >20 minutes but <12 hours in duration. If the symptom duration at the time of evaluation was <1 hour, to rule out unstable angina, the symptoms had to be unresponsive to glyceryl trinitrate (GTN) (i.e. ongoing) prior to signing the informed consent. Patients with symptom onset within 12 hours, in whom the symptoms lasted >1 hour but subsequently resolved still may have been enrolled if the ECG, at the time of the evaluation, showed definite ongoing ST segment elevation.

3. ECG criteria: ST-segment elevation of ≥1 mm in ≥2 contiguous leads, or (presumably new) left bundle branch block, or true posterior MI with ST depression of ≥1 mm in ≥2 contiguous anterior leads.

Main Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the trial:

1. Known hypersensitivity or contraindication to any of the following substances: Heparin, pork, or pork products, abciximab and eptifibatide, aspirin, clopidogrel and ticlopidine, bivalirudin, paclitaxel or TaxolTM, polymer components of the TAXUS™ stent (SIBS), stainless steel, contrast media (patients with documented sensitivity to contrast who could be effectively premedicated with steroids and diphenhydramine (e.g. rash) may have been enrolled. Patients with true anaphylaxis to prior contrast media, however, were not to be enrolled).
2. Prior administration of thrombolytic therapy, bivalirudin, GP IIb/IIIa inhibitors, low molecular weight heparin or fondaparinux for this admission. Patients receiving prior UFH may have been enrolled, and treated per randomisation.
3. Current use of warfarin. Systemic (intravenous [IV]) Paclitaxel or Taxol use within 12 months.
4. History of bleeding diathesis or known coagulopathy (including heparin-induced thrombocytopenia), or refused blood transfusions, history of intra-cerebral mass, aneurysm, arteriovenous malformation, or haemorrhagic stroke.
5. Stroke or transient ischaemic attack within the past 6 months, or any permanent residual neurologic defect.
6. Gastrointestinal or genitourinary bleeding within the last 2 months, or major surgery within 6 weeks.
7. Recent history or known current platelet count <100,000 cells/mm3 or haemoglobin <10 g/dL (note: baseline laboratories did not have to be available prior to enrolment).
8. Extensive peripheral vascular disease, such that emergent angiography and intervention in the opinion of the investigator was likely to be difficult or complicated.
9. An elective surgical procedure was planned that would have necessitated interruption of thienopyridines during the first 6 months post enrolment.

*Treatments*

Patients were to be enrolled in a 1:1 fashion in the emergency room (ER) to anticoagulation with UFH plus routine GP IIb/IIIa inhibition or bivalirudin and provisional GP IIb/IIIa inhibition using a dynamic allocation algorithm through an Interactive Voice Response System (IVRS).

Bivalirudin treatment was begun with an intravenous (IV) bolus of 0.75 mg/kg and an infusion of 1.75 mg/kg/h. If pre-randomisation heparin was administered, bivalirudin was begun 30 minutes later after discontinuation of heparin. Bivalirudin was discontinued per protocol at the completion of angiography or PCI or could be continued at operator discretion. If needed, a post-PCI bivalirudin infusion was permitted at a dose of 0.25 mg/kg/h (with or without an IV bolus of 0.10 mg/kg) if the infusion had previously been interrupted for >2 hours to remove the sheaths. The study protocol also took into account differences between the US package insert and EU summary of product characteristics (SPC) for Angiox® with respect to dose adjustments for renal impairment. In the EU, in patients with moderate renal impairment (glomerular filtration rate [GFR]: 30-59 mL/min) the infusion dose was to be adjusted to 1.4 mg/kg/h, whereas in the US this was not required. Based on the EU SPC patients with known severe renal impairment (GFR <30 mL/min) and dialysis dependant patients were excluded.

Treatment with UFH was dosed as 60 U/kg of IV heparin. GP IIb/IIIa inhibitors were started as soon as was logistically feasible (ideally in the ER). Either abciximab or eptifibatide (double bolus, with the first bolus given at least 3 minutes prior to PCI and the second bolus given 10 minutes after the first) were to be used with the choice left to the discretion of the operator. For patients with a known baseline serum creatinine >2.0 mg/dL, abciximab was recommended.

Patients randomised to bivalirudin were permitted to be administered a provisional GP IIb/IIIa inhibitor (abciximab bolus plus 12-hour infusion or eptifibatide double bolus plus 12- to 18-hour infusion) during primary PCI for the following 2 predefined reasons only:

• The presence of a “giant” thrombus adjacent to the stent or in the coronary vessel (diameter >2 times that of the coronary vessel) after PCI in the absence of a mechanical obstruction.

• Sustained no reflow (TIMI 0-1 flow in the absence of a mechanical obstruction, refractory to either intracoronary nitroprusside, adenosine or a calcium channel blocker delivered intracoronary to the distal coronary bed via an infusion catheter).

*Objectives*

The key objectives of the pharmacology randomisation were that treatment with bivalirudin resulted in:

• Similar or reduced rates of net adverse clinical events (NACE), defined as the composite of MACE plus major bleeding, at 30 days (primary endpoint).
• Similar rates of MACE and its individual components (death, reinfarction, ischaemic TVR, and stroke) at 30 days (key efficacy endpoint).
• Similar or reduced rates of major bleeding events (protocol definition [ACUITY scale]) at 30 days (primary safety endpoint).

*Outcomes/endpoints*

The primary endpoint was a composite endpoint (NACE, Net adverse clinical event) which combined MACE (Major Adverse Ischaemic Cardiac Events: death, reinfarction, stroke or ischaemic TVR, key efficacy endpoint) with major bleeding (primary safety endpoint). The components were defined as follows:

Death: included death from any cause, and the cause of death (cardiac vs. non-cardiac) was adjudicated. If the cause of death could not be adjudicated, the most severe cause was assigned.

Reinfarction: when one of the following criteria was met:

Reinfarction during medical therapy (not procedure induced)

In patients with normal baseline levels of troponin or creatine kinase-myocardial band (CK-MB) (or creatine phosphokinase [CPK] in the absence of CK-MB):

• Recurrent chest pain or ischaemic equivalent symptoms lasting ≥30 minutes.
AND
• A new elevation of troponin or CK-MB >upper limit of normal (ULN) (or CPK >ULN in the absence of CK-MB). Enzyme or biomarker elevations alone without symptoms did not represent a myocardial infarction (MI).

In patients with elevated baseline levels of troponin or CK-MB (or CPK in the absence of CK-MB) that were documented to be falling:

• Recurrent chest pain or ischaemic equivalent symptoms lasting ≥30 minutes.
AND
• A rise of troponin or CK-MB >ULN (or CPK >ULN in the absence of CK-MB) above the previous nadir level.

In patients with elevated baseline levels of troponin or CK-MB (or CPK in the absence of CK-MB), for whom the peak CK-MB (or CPK) had not yet been reached:

• Recurrent chest pain or ischaemic equivalent symptoms lasting ≥30 minutes.

Reinfarction following PCI

In patients with normal baseline levels of CK-MB (or CPK in the absence of CK-MB):

• A new elevation of troponin or CK-MB >3x ULN (or CPK >3x ULN in the absence of CK-MB) within 24 hours post PCI.

In patients with elevated baseline levels of CK-MB (or CPK in the absence of CK-MB) that were documented to be falling:

• Recurrent chest pain or ischaemic equivalent symptoms lasting ≥30 minutes.
AND
• An absolute rise of CK-MB >3x ULN (or an absolute rise in CPK >2x ULN in the absence of CK-MB) above the previous nadir level within 24 hours post PCI.

In patients with elevated baseline levels of CK-MB (or CPK in the absence of CK-MB), but peak CK-MB (or CPK) had not yet been reached:

• Recurrent chest pain or ischaemic equivalent symptoms lasting ≥30 minutes.
AND
• New ECG changes consistent with reinfarction (only necessary or valid in the absence of left bundle branch block, Wolff Parkinson White syndrome, paced rhythm or other artefact that would preclude electrocardiographic definition of MI).
AND
• The next CK-MB (or CPK) level measured approximately 8-12 hours after the event was at least 50% above the previous level or >3x ULN, whichever was greater.

MI following coronary artery bypass graft (CABG) in patients undergoing CABG, diagnosis of MI required:

• Any CK-MB ≥10x ULN (or CPK ≥10x ULN in the absence of CK-MB) within 24 hours of CABG and was at least 50% above the most recent pre-CABG levels.
OR
• Any CK-MB ≥5x ULN (or CPK ≥5x ULN in the absence of CK-MB) within 24 hours of CABG and was at least 50% above the most recent pre-CABG levels AND new, significant (≥0.04 seconds) Q-waves in ≥2 contiguous ECG leads.

Q-wave and non-Q-wave MI All reinfarctions were adjudicated as being either Q-wave (development of new pathologic Q-waves in 2 or more contiguous leads) or non-Q-wave.

Ischaemic TVR: any ischaemia-driven repeat PCI of the target vessel or bypass surgery of the target vessel. The target vessel consists of the target lesion(s) plus any additional lesions in the main epicardial coronary artery or branches containing the target lesion (the left anterior descending artery, left circumflex coronary artery or right coronary artery).

Stroke: an acute neurological deficit resulting in death or lasting for more than 24 hours, as classified by a physician, with supporting information, including brain images and neurological/neurosurgical evaluation.

Major bleeding**:** Major bleeding as previously defined in the ACUITY trial was the occurrence of any of the following: intracranial bleeding, intraocular bleeding, retroperitoneal bleeding, access site haemorrhage requiring surgery or a radiological or interventional procedure, haematoma ≥5 cm in diameter at the puncture site, reduction in haemoglobin concentration of ≥4 g/dL without an overt source of bleeding, reduction in haemoglobin concentration of ≥3 g/dL with an overt source of bleeding, re-operation for bleeding, or use of any blood product transfusion.
Major bleeding according to the protocol definition was adjudicated as non-CABG related.

*Sample size*

The trial was powered for two independent randomisations (pharmacology randomisation and stent randomisation). The 30-day endpoints of net adverse clinical events (NACE) and non-CABG related major bleeding (related to the pharmacology randomisation) were different in timing and mechanism from the one-year endpoint of ischaemic TVR (related to the stent randomisation), thus no statistical correction for multiple comparisons was required. There was hierarchical sequential non-inferiority and superiority testing of NACE and major bleeding. Non-inferiority was declared if the upper limit of the CI on the difference in event rates did not exceed the non-inferiority margin. Expected event rates,

non-inferiority margins (δ) and power calculations for the primary (pharmacology) randomisation are detailed in the following table:

Power Calculations (HORIZONS study)

| Endpoint | Superiority event rates | | Non-inferiority | | Superiority |
|---|---|---|---|---|---|
| | Bivalirudin | UFH + GP IIb/IIIa | δ [a] | Power | Power |
| MACE | 5.0% | 5.0% | 2.2% | 82% | Not applicable |
| Major Bleeding | 6.0% | 9.0% [b] | 1.0% | 99% | 90% |
| NACE | 9.0% | 12.0% [b] | 3.2% | 80% | 80% |

MACE = major adverse ischaemic cardiac events; NACE = net adverse clinical events.
[a] Non-inferiority margin for the absolute difference between treatment arms.
[b] Event rates used for non-inferiority.
Source: HORIZONS CSR, Section 9.7.2

*Randomisation*

Randomisation was stratified by use of any non protocol pre-procedural heparin prior to randomisation (yes/no), by loading dose of thienopyridines (clopidogrel 300 mg or 600 mg, or ticlopidine 500 mg), by GP IIb/IIIa inhibitor to be given (abciximab or eptifibatide), and by site (US or non-US).

*Blinding (masking)*

The study is single blind. The following strategies were used to minimise bias related to the study:

- All Core Labs (Angiographic, IVUS, and ECG) were blinded to the pharmacological and stent randomisations.
- An independent clinical events committee (CEC) adjudicated all primary and secondary clinical endpoints. The committee members and the CEC management team were completely blinded to the stent and drug arms, as well as any patient identifying information. The CEC adjudicated the events based on predetermined definitions.
- Patients were blinded to the type of stents implanted and pharmacological agents administered.
- Clinical follow-up visits (including follow-up phone calls) were conducted by a physician/nurse/research personnel other than those involved in the baseline procedure, whenever possible, to reduce the potential for investigator bias.
- The endpoints of death, reinfarction, stroke, bleeding, and stent thrombosis were based on laboratory tests, imaging studies, ECGs, angiograms, documented clinical events, or abnormal physical exams, all of which were verified by blinded CEC review of copies of the original source documentation, ensuring that ascertainment bias would be minimal.

*Statistical methods*

All statistical analyses were performed using SAS statistical software (Version 9.1).

For categorical variables, the number and percentage within each category of the parameter were calculated. Confidence intervals for the differences were calculated using the normal approximation to the binomial with the Fleiss continuity correction. Confidence intervals of the RRs were also calculated using the normal approximation. Categorical variables were compared between treatment arms by the Chi-square or Fisher's exact test, as appropriate (i.e. if any expected cell counts were less than 5, then the non-parametric Fisher's exact test was used).

For continuous variables, the following descriptive statistics were calculated: mean, median, standard deviation (SD), interquartile range (IQR), i.e. 25 and 75 percentiles (Q1 and Q3, respectively), minimum, and maximum were calculated. Time-to-event data were displayed using Kaplan-Meier (KM) methodology. Kaplan-Meier estimates and Cox proportional hazard ratios (HRs) were presented and compared between treatment arms using the log rank test.

All statistical tests were performed at the 2-sided significance level of 0.05, unless otherwise specified. Tests of non-inferiority were performed at a 1-sided significance level of 0.025.

The analysis of each of the study endpoints was not covariate adjusted. However, subgroup analyses were conducted to examine potential influential factors.

No imputation methods were used to infer missing values. For the categorical analysis of clinical study endpoints, patients lost to follow-up were included in the denominator for the statistical analyses of event rate proportions and were considered to be non-events. In addition, 2 sensitivity analyses were performed to assess the impact of missing values from patients lost to follow-up on the primary and major secondary study endpoints: a complete case analysis which excluded patients lost to follow-up and an analysis assuming that all patients lost to follow-up prior to Day 23 were events.

For all other analyses, only available data were analysed. For time-to-event analyses, dropouts were censored at their last known status time.

The follow-up time window for the 30-day endpoint was ±7 days according to protocol. Any 30-day visits outside this window were noted as a protocol deviation. However, only events occurring up to and including 30 days were reported for the event rate endpoints. Actual event dates/times were used for all endpoint analyses. Since the ascertainment of the endpoint event time could be made regardless of the time of follow-up, data may have been backfilled from subsequent visits for endpoint determination. For example, if a patient without a 30-day follow-up had a 6 month follow-up visit during which ascertainment of clinical status was made, then the 6-month follow-up information was used to replace the 30-day visit. Patients who had no event and no follow-up information available during the 30 ±7-day window (including any backfilled information, i.e. the last follow-up time occurring prior to 23 days) were considered as missing for follow-up, though they were included in the intent-to-treat (ITT) population and were considered to be non-events for the event rate endpoint analysis.

For time-to-event analyses, patients were censored at their last available follow-up (see Section 9.7.1.1.2). Kaplan-Meier estimates at exactly 30 days were presented, and HRs and 95% CIs were constructed using all events occurring up to Day 30.

Interim Analyses and Data Monitoring: The DSMB was responsible for review of the interim data and identification of any potential safety issues. The DSMB reviewed safety and efficacy endpoints. Members of the DSMB met before the trial started to decide the meeting schedule and to review the protocol, stopping rules, and the logistics of reporting the safety data. The DSMB met again when 250 patients were enrolled and their 30 day follow-up data was available. The next meeting occurred after 500 patients were enrolled. The DSMB met approximately every 6 months afterwards until enrolment was completed. The frequency of DSMB meetings was subject to change at the discretion of the members. Semi-blinded data were presented to the DSMB at each meeting. The DSMB members were blinded to the identity of the treatment arms. Unblinded data were made available for the DSMB only if the DSMB members decided accordingly (the data was provided in sealed envelopes by IVRS to the Cardiovascular Research Foundation biostatistician). The DSMB chairman was also notified within 24 hours of any fatal or life-threatening unexpected SAE.

A test for treatment by site interaction was done for (a) EU vs. non EU sites and (b) US vs. non US sites for all primary and major secondary endpoints.

No multiplicity adjustments were made for the 2 separate and independent randomisations. Sequential hierarchical endpoint testing for the 2 primary endpoints was used to control the overall α level. The primary endpoint of NACE and the primary safety endpoint of major bleeding were tested hierarchically for non-inferiority and subsequently for superiority on the same population. The order of analyses was:

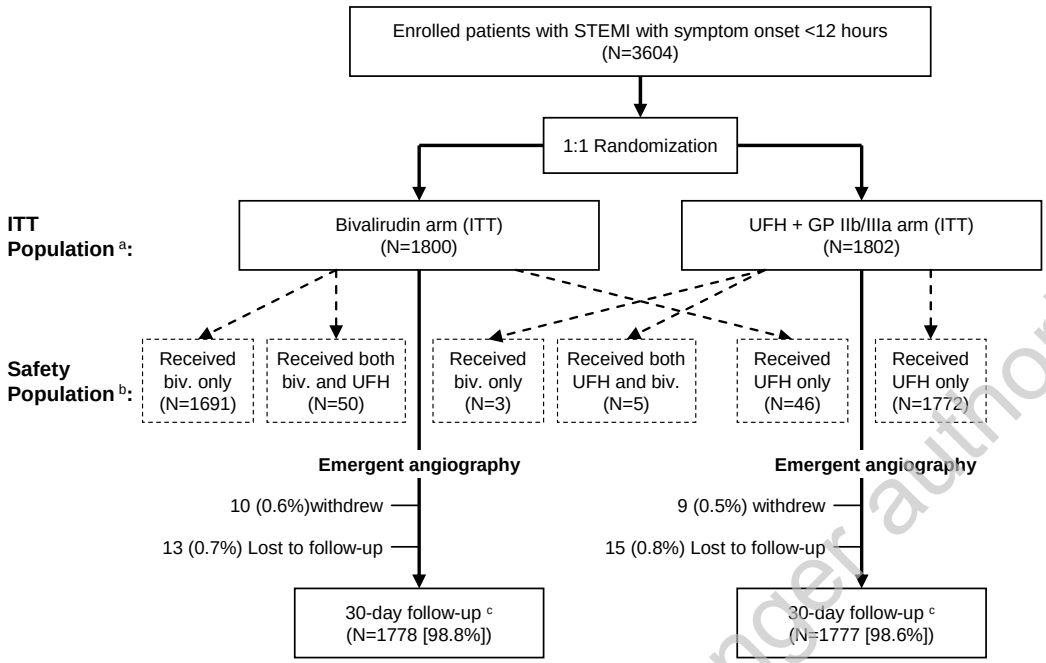
1. Non-inferiority test of NACE.
2. Non-inferiority test of Major Bleeding.
3. Superiority test of Major Bleeding.
4. Superiority test of NACE.

An inferential non-inferiority test for MACE was planned in the protocol.

*Results*

Participant flow

**Disposition of patients in the HORIZONS study**




Biv = bivalirudin; ITT = intent-to-treat; N = total number of patients; STEMI = ST segment elevation myocardial infarction.
[a] Patients 1062001 and 1072001, both randomised to the bivalirudin arm, were excluded from the ITT population due to missing informed consent.
[b] Thirteen patients in the bivalirudin arm and 22 patients in the UFH plus GP IIb/IIIa did not receive any study medication.
[c] Includes patients with 1-month or any follow-up visit after Day 23 or with any MACE event.
Source: HORIZONS CSR, Section 15.1, Table 1.1.1

*Numbers analysed*

All primary and major secondary endpoints were analysed both on an ITT basis and on a PP basis. The primary statistical analysis was based on the ITT population.

ITT population: all patients, who signed the written informed consent form, were randomised into the study and were not withdrawn for study reasons (randomisation occurred in error, patient was double randomised, or technical error), regardless of whether or not the treatment the patient was randomised to was actually administered.

PP population: enrolled patients with "true MI" and no major protocol violations, who actually received the assigned treatment. Patients randomised to the UFH plus GP IIb/IIIa arm were excluded from the PP population if they did not receive any heparin or if they underwent angioplasty and did not receive a GP IIb/IIIa inhibitor without a valid reason to withhold such therapy, such as the interval development of bleeding. Patients not receiving a GP IIb/IIIa inhibitor after control angiography because of intended medical therapy or surgery, or in whom bleeding or another complication developed necessitating withholding these medications prior to their administration were included in the PP population. Patients randomised to the bivalirudin arm were excluded from the PP population if they did not receive any bivalirudin or did receive a GP IIb/IIIa inhibitor for either routine upfront use or for provisional use not meeting one of the protocol specified criteria. Patients receiving provisional GP IIb/IIIa inhibitor for one of the protocol specified criteria of thrombotic procedural complications were included in the PP population.

Major protocol violations which resulted in a patient being excluded from the PP population were as follows:

- Any of the clinical inclusion criteria were not present.
- Any of the clinical exclusion criteria were present.

• Aspirin was not given prior to angioplasty as per the protocol procedures (unless the patient was taking aspirin regularly at home prior to admission).
• A thienopyridine agent was not given prior to angioplasty as per the protocol procedures (unless the patient was taking a thienopyridine regularly at home prior to admission).

Safety population: patients in the ITT population are assigned to the treatment actually received. For this safety analysis, patients receiving any post-randomisation bivalirudin were analysed in the bivalirudin arm. All other patients were analysed in the UFH plus GP IIb/IIIa arm, if any heparin was administered either before or after randomisation.

PCI population: all ITT patients who underwent index PCI.

*Ancillary analyses*

A total of 22 subgroups were examined in an exploratory fashion and the interactions of treatment with subgroups were tested to identify differing treatment effects in these subgroups with regard to the key clinical efficacy endpoints (i.e. MACE and NACE). An interaction value of $p<0.0028$ was used to identify a significant finding [Lagakos 2006].

Only for the subgroup of time from symptom onset to study hospital ER admission was an interaction p-value of less than the unadjusted nominal α of 0.05 observed (p=0.0254). The difference in MACE rates was statistically significant in patients with a time from symptom onset to study hospital ER admission of ≤2.2 hours (5.8% bivalirudin vs. 3.3% UFH plus GP IIb/IIIa; p=0.0306) and not statistically significant in the complimentary group (5.3% vs. 6.6%; p=0.3433).

Supportive study

- **BIAMI STUDY**

*Study design*

BIAMI was a multicenter, open-label, uncontrolled, single-arm study in patients with STEMI within 12 hours of symptom onset undergoing primary PCI. All patients received bivalirudin as the anticoagulant during the in-hospital period and were followed up at Day 7/discharge, 30 days and 6 months. The use of the GP IIb/IIIa inhibitor abciximab was on a provisional basis in the event of TIMI flow <3 at the end of the PCI procedure. PCI was performed according to standard institutional practice.

*Objectives*

The primary objective of the study was to assess safety. Primary safety endpoints evaluated at 7 days were clinically significant bleeding (defined as intracranial, intraocular, or retroperitoneal bleeding, access site haematoma requiring intervention or >5 cm, reduction in haemoglobin >3 g/dL with overt bleeding, any blood transfusion, or any reoperation for bleeding) and thrombocytopenia (<100,000 cells/μL with a fall of >50% from baseline). AEs were also assessed to evaluate safety. Efficacy endpoints evaluated at 7 and 30 days and 6 months were the composite and individual components ofdeath (all cause), reinfarction, repeat intervention/TVR as a result of ischaemia, disabling stroke, and subacute thrombosis (at 7 and 30 days only). All analyses were done descriptively.

There were 201 patients enrolled at 13 centres in the US between 12 April 2004 and 23 May 2005. There were 5 (2.5%) patients who withdrew between Day 7 and the Day 30 follow-up and 6 (3.1%) patients between Day 30 and the 6-month follow-up. The population was predominantly white (87.1%) and male (69.2%) with a median age of 58 years (rangebetween 31 to 92 years) and a median weight of 84 kg (range: 47 to 152 kg).

Up to Day 7/discharge, the primary composite endpoint occurred in only 5 (2.5%) patients, and by 30 days, a further 5 ischaemic events had occurred in 4 patients. At 6 months, 8 more patients experienced 12 additional ischaemic events, for a total incidence of 8.9% (17/191 patients); 7 patients died, 6 experienced a reinfarction, 8 required TVR, and 2 had a stroke. The type of stent used did not appear to have any correlation with ischaemic outcome.

Clinically significant bleeding occurred in 6 (3.0%) patients at Day 7/discharge. Up to Day 7/discharge, 3 (1.5%) patients developed thrombocytopenia. The combined rate of TIMI-defined bleeding was 6.0% (12/201) at Day 7/discharge; TIMI-defined bleeding was reported as major in 5 (2.5%) patients and minor in 7 (3.5%) patients. A non-CABG transfusion was required by 5 (2.5%) patients. Analysis performed across trials (pooled analyses and meta-analysis.

## 1.3 Clinical safety

HORIZON Study

The safety objectives of the pharmacology randomisation were to demonstrate that in patients with STEMI undergoing a primary PCI strategy bivalirudin after 30 days compared to UFH plus routine use of GP IIb/IIIa inhibitors, resulted in similar or reduced rates of major bleeding events (protocol definition [ACUITY scale]) at 30 days (primary safety endpoint), and to compare:

- Stent thrombosis at 30 days, defined by the ARC definitions.
- Site reported minor bleeding as well as bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria.
- Investigator reported AEs.

*Patient exposure*

All safety endpoints were analysed using the safety population in which patients in the intent-to-treat (ITT) population were assigned to the treatment actually received. For this safety analysis, patients receiving any post-randomisation bivalirudin were analyzed in the bivalirudin arm (n=1749). All other patients were analyzed in the UFH plus GP IIb/IIIa arm, if any heparin was administered either before or after randomization (n=1818). Patients not receiving any study drug were excluded from the safety population.

*Non-CABG major bleeding events*

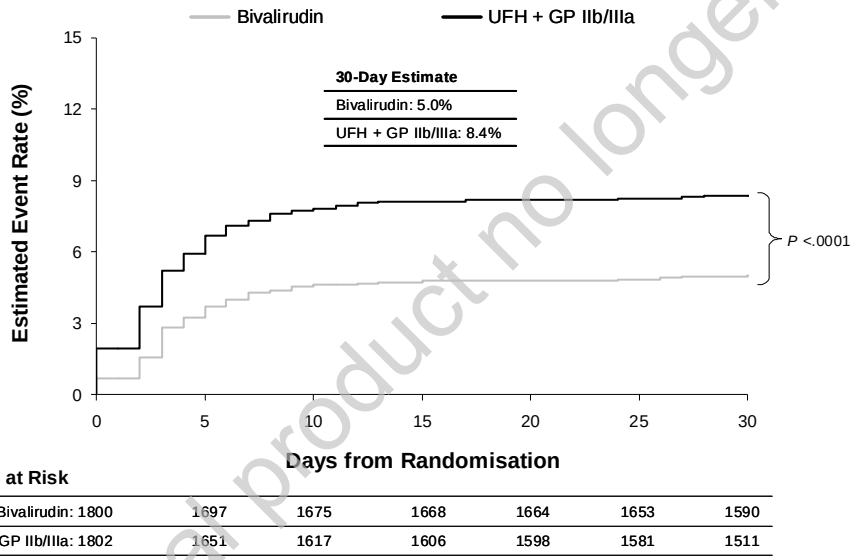
Defined as: intracranial bleeding, intraocular bleeding, retroperitoneal bleeding, access site haemorrhage requiring surgery or a radiologic or interventional procedure, haematoma ≥5 cm in diameter at the puncture site, reduction in haemoglobin concentration of ≥4 g/dL without an overt source of bleeding, reduction in haemoglobin concentration of ≥3 g/dL with overt bleeding, re-operation for bleeding, or any blood product transfusion.

Table 1 Event rates of major bleeding at 30 days in the HORIZONS study

| Population | n/N (%) of patients | | Estimate [95% CI] | | |
|---|---|---|---|---|---|
| | Bivalirudin | UFH + GP IIb/IIIa | Difference | Relative Risk | P-value [a] |
| ITT | 89/1800 (4.9) | 149/1802 (8.3) | -3.3 [-5.0, -1.6] | 0.60 [0.46, 0.77] | <0.0001 |
| Safety | 85/1749 (4.9) | 152/1818 (8.4) | -3.5 [-5.2, -1.8] | 0.58 [0.45, 0.75] | <0.0001 |
| PCI | 85/1678 (5.1) | 142/1662 (8.5) | -3.5 [-5.2, -1.7] | 0.59 [0.46, 0.77] | <0.0001 |

CI = confidence interval; ITT = intent-to-treat; n = number of respective patients; N = total number of patients; PCI = percutaneous coronary intervention.
Note: Non-inferiority is indicated with the upper limit of the 95% CIs being less than δ=1.0%.
[a] P-value for superiority from chi-square test.
Source: HORIZONS CSR, Section 15.2, Tables 3.1.2.1.1, 3.1.2.1.2, and 2.1

Figure 2 30-Day Kaplan-Meier plot of major bleeding in the HORIZONS study (ITT population)




Note: 30-day estimates based on KM methodology and p-value based on log-rank test.
Source: HORIZONS CSR, Section 15.3, Table 3.2.1

To check the robustness of the results from the primary safety analysis, analyses were repeated using major bleeding events excluding ≥5 cm haematomas and using non-access site major bleeding events only, i.e. intracranial bleeding, intraocular bleeding, and decrease in haemoglobin ≥4 g/dL without an overt source. Results are summarised below:

Table 2 Sensitivity analyses of major bleeding at 30 days in the HORIZONS study

| Population | n/N (%) of patients | | Estimate [95% CI] | | |
|---|---|---|---|---|---|
| | Bivalirudin | UFH + GP IIb/IIIa | Difference | Relative Risk | P-value [a] |
| **Excluding haematoma ≥5 cm events** | | | | | |
| ITT | 84/1800 (4.7) | 140/1802 (7.8) | -3.1 [-4.7, -1.5] | 0.60 [0.46, 0.78] | 0.0001 |
| Safety | 81/1749 (4.6) | 142/1818 (7.8) | -3.2 [-4.8, -1.5] | 0.59 [0.45, 0.77] | <0.0001 |
| **Non-access site major bleeding** | | | | | |
| ITT | 45/1800 (2.5) | 79/1802 (4.4) | -1.9 [-3.1, -0.6] | 0.57 [0.40, 0.82] | 0.0019 |
| Safety | 43/1749 (2.5) | 80/1818 (4.4) | -1.9 [-3.2, -0.7] | 0.56 [0.39, 0.80] | 0.0015 |

CI = confidence interval; ITT = intent-to-treat; n = number of respective patients; N = total number of patients.

[a] P-value for superiority from chi-square test.

Source: HORIZONS CSR, Section 15.3, Tables 3.1.2.1.1 and 3.1.2.1.2.

Major and minor TIMI bleeding

| | |
|---|---|
| TIMI major bleeding | Intracranial bleeding or bleeding associated with a decrease in haemoglobin ≥5 g/dL (or ≥15% of haematocrit) |
| TIMI minor bleeding | Observed bleeding: ≥3 g/dL decrease in the haemoglobin concentration (or ≥9% decrease in haematocrit) |
| | No bleeding observed: ≥4 g/dL decrease in the haemoglobin concentration (or ≥12% decrease in haematocrit) |

Table 3 Event rates of non-CABG TIMI bleeding at 30 days in the HORIZONS study (Safety population)

| TIMI Category | Number (%) of patients | | Estimate [95% CI] | | |
|---|---|---|---|---|---|
| | Bivalirudin (N = 1749) | UFH + GP IIb/IIIa (N = 1818) | Difference | Relative Risk | P-value [a] |
| Major | 29 (1.7) | 54 (3.0) | -1.3 [-2.4, -0.3] | 0.56 [0.36, 0.87] | 0.0094 |
| Minor | 41 (2.3) | 75 (4.1) | -1.8 [-3.0, -0.6] | 0.57 [0.39, 0.83] | 0.0027 |
| Major or minor | 70 (4.0) | 130 (7.2) | -3.1 [-4.7, -1.6] | 0.56 [0.42, 0.74] | <0.0001 |

CI = confidence interval; N = total number of patients; TIMI = thrombolysis in myocardial infarction.

[a] P-value from chi-square test.

Source: HORIZONS CSR, Section 15.3, Tables 3.1.2.1.2

GUSTO bleeding Severe or life-threatening: Either intracranial haemorrhage or bleeding that causes haemodynamic compromise and requires intervention. Moderate: Bleeding that requires blood transfusion but does not result in haemodynamic compromise

Table 4 Event rates of GUSTO bleeding at 30 days in the HORIZONS study (Safety population)

| GUSTO Category | Number (%) of patients | | Estimate [95% CI] | | |
|---|---|---|---|---|---|
| | Bivalirudin (N = 1749) | UFH + GP IIb/IIIa (N = 1818) | Difference | Relative Risk | P-value [a] |
| Severe/Life-threatening | 7 (0.4) | 12 (0.7) | -0.3 [-0.8, 0.3] | 0.61 [0.24, 1.54] | 0.2865 |
| Moderate | 51 (2.9) | 93 (5.1) | -2.2 [-3.5, -0.9] | 0.57 [0.41, 0.80] | 0.0008 |
| Mild | 55 (3.1) | 106 (5.8) | -2.7 [-4.1, -1.3] | 0.54 [0.39, 0.74] | 0.0001 |
| Severe/Life-threatening or moderate | 58 (3.3) | 104 (5.7) | -2.4 [-3.8, -1.0] | 0.58 [0.42, 0.79] | 0.0006 |

CI = confidence interval; GUSTO = global use of strategies to open occluded coronary arteries; N = total number of patients.

[a] P-value from chi-square test.

Source: HORIZONS CSR, Section 15.3, Tables 3.1.2.1.2

Stent Thrombosis

Following the ARC definition, stent thrombosis was the occurrence of any of the following:

- Clinical presentation of ACS with angiographic evidence of stent thrombosis (the angiographic appearance of thrombus adjacent to a previously treated target lesion) = DEFINITE stent thrombosis.
- In the absence of angiography, any unexplained death or Q-wave myocardial infarction (MI) in the distribution of the target lesion were considered a surrogate of stent thrombosis = PROBABLE stent thrombosis.

Among the 3567 patients of the safety population, the overall rate of stent thrombosis at 30 days was not significantly different between the bivalirudin and the UFH plus GP IIb/IIIa arms (2.3% bivalirudin vs. 1.9% UFH plus GP IIb/IIIa, p=0.3239), as shown in Table 5. However, within the first 24 hours, stent thrombosis developed in 19 more patients in the bivalirudin arm than in the UFH plus GP IIb/IIIa arm (1.3% vs. 0.2%, p=0.0002), whereas between 24 hours and 30 days, stent thrombosis occurred in 11 fewer patients in the bivalirudin arm than in the UFH plus GP IIb/IIIa arm (1.1% vs. 1.7%, p=0.1481). Of the 93 deaths in the ITT population, 19 occurred after stent thrombosis: 2 after acute stent thrombosis (Patient 4507037 in the bivalirudin arm and Patient 7005003 in the UFH plus GP IIb/IIIa arm) and 17 after subacute stent thrombosis, 3 in the bivalirudin arm and 14 in the UFH plus GP IIb/IIIa arm. Results from an analysis based on the ITT population were similar to those based on the safety population.

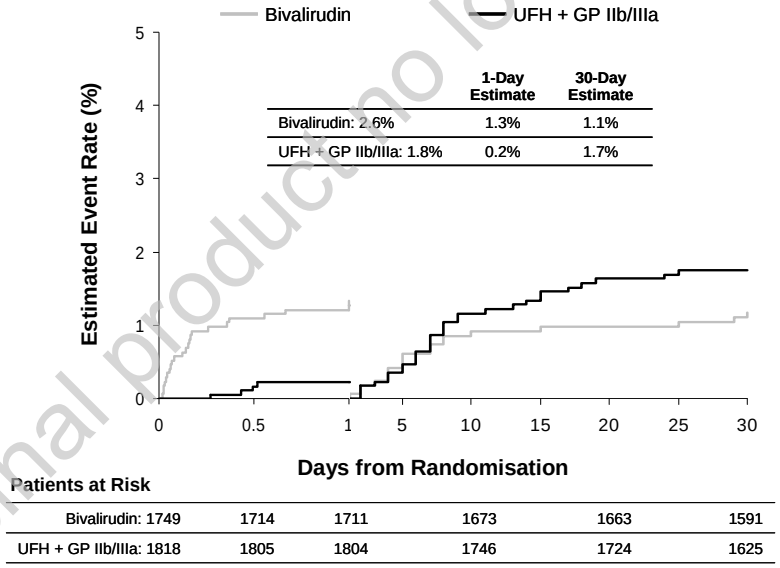
Table 5 Event Rates of Stent Thrombosis Events at 30 Days in the HORIZONS study (Safety population)

| Category | Number (%) of patients | | Estimate [95% CI] | | |
|---|---|---|---|---|---|
| | Bivalirudin (N = 1749) | UFH + GP IIb/IIIa (N = 1818) | Difference | Relative Risk | P-value [a] |
| Any Stent Thrombosis (ARC) | 41 (2.3) | 34 (1.9) | 0.5 [-0.5, 1.5] | 1.25 [0.80, 1.97] | 0.3239 |
| Acute | 23 (1.3) [b] | 4 (0.2) | 1.1 [ 0.5, 1.7] | 5.98 [2.07, 17.25] | 0.0002 |
| Subacute | 19 (1.1) [b] | 30 (1.7) | -0.6 [-1.4, 0.3] | 0.66 [0.37, 1.17] | 0.1481 |

ARC = academic research consortium; CI = confidence interval; N = total number of patients.
[a] P-value from chi-square test.
[b] Patient 1082002 in the bivalirudin arm had both an acute and a subacute stent thrombosis.
Source: HORIZONS CSR, Section 15.3, Tables 3.1.2.1.2

Figure **3**3 shows a set of KM curves for the first 24 hours (time to acute stent thrombosis) and another for the remainder of the interval (time to subacute stent thrombosis) and demonstrates the early difference (≤24 hours) in favour of UFH plus GP IIb/IIIa in contrast to the later difference (24 hours to 30 days) in favour of bivalirudin.

Figure 3 30-Day Kaplan-Meier plot of stent thrombosis in the HORIZONS study (Safety population)




Note: 30-day estimates based on KM methodology and p-values based on log-rank test.

Additional exploratory analyses were performed to further investigate the finding described above for stent thrombosis during the first 24 hours. Of the 23 patients in the bivalirudin arm with a stent thrombosis within the first 24 hours, 15 had other possible influencing factors including diabetes mellitus (2 patients), TIMI 2 flow post PCI (3 patients), no loading with clopidogrel (3 patients), low cardiac output state (Killip-2) (1 patient), treatment of a side branch (2 patients), major bleeding (3 patients), or bolus only dosing of bivalirudin (1 patient).

*Thrombocytopenia*

Significantly fewer thrombocytopenia events occurred in the bivalirudin arm (1.4%) than in the UFH plus GP IIb/IIIa arm (3.9%; p<0.0001), as shown in Table 6. The majority of events were mild in intensity. Severe thrombocytopenia was only reported in the UFH plus GP IIb/IIIa arm (7 patients [0.4%]).

**Table 6 Event rates of thrombocytopenia events at 30 days in the HORIZONS study (Safety population)**

| Category | n/N (%) of patients | | Estimate [95% CI] | | |
|---|---|---|---|---|---|
| | Bivalirudin | UFH + GP IIb/IIIa | Difference | Relative Risk | P-value [a] |
| Thrombocytopenia [b] | 23/1635 (1.4) | 67/1701 (3.9) | -2.5 [-3.7, -1.4] | 0.36 [0.22, 0.57] | <0.0001 |
| Mild | 17/1635 (1.0) | 48/1701 (2.8) | -1.8 [-2.8, -0.8] | 0.37 [0.21, 0.64] | 0.0002 |
| Moderate | 6/1635 (0.4) | 12/1701 (0.7) | -0.3 [-0.9, 0.2] | 0.52 [0.20, 1.38] | 0.1822 |
| Severe | 0/1635 (0.0) | 7/1701 (0.4) | -0.4 [-0.8, -0.0] | Not applicable | 0.0157 |

CI = confidence interval; n = number of respective patients; N = total number of patients.

[a] P-value from chi-square test except for severe thrombocytopenia events where Fisher's exact test was applied.

[b] Includes heparin induced thrombocytopenia.

Source: HORIZONS CSR, Section 15.3, Tables 3.1.3.2

**Table 7 Overview of adverse events in the HORIZONS study (Safety population)**

| Type of AE | Number (%) of patients | | | |
|---|---|---|---|---|
| | Bivalirudin (N=1749) | UFH + GP IIb/IIIa (N=1818) | Total (N=3567) | p-value [a] |
| Any AE | 956 (54.7) | 1044 (57.4) | 2000 (56.1) | 0.0961 |
| AE related to study drug | 150 (8.6) | 274 (15.1) | 424 (11.9) | <0.0001 |
| Serious AE | 267 (15.3) | 311 (17.1) | 578 (16.2) | 0.1358 |
| Serious AE related to study drug | 25 (1.4) | 41 (2.3) | 66 (1.9) | 0.0673 |
| Serious AE leading to study discontinuation | 13 (0.7) | 11 (0.6) | 24 (0.7) | 0.6137 |

AE = adverse event; N = total number of patients.

[a] P-value from chi squared test.

Source: HORIZONS CSR, Section 15.3, Table 3.1.7.0.2

*Laboratory findings*

At baseline, all laboratory parameters were comparable between treatment arms. Differences between treatment arms were observed in the number of patients with a post catheterisation haemoglobin value of <10 g/dL and those with a post catheterisation haemoglobin decrease of ≥25% below baseline. For both these categories the frequency was lower in the bivalirudin arm than in the UFH plus GP IIb/IIIa arm (6.7% bivalirudin vs. 9.8% UFH plus GP IIb/IIIa, and 6.4% vs. 11.8%, respectively). Post catheterisation creatinine levels were similar between treatment arms. Results of haematology laboratory parameters at baseline and post catheterisation were similar between the ITT and safety populations.

*Safety in special populations*

The 18 most relevant subgroups were examined in an exploratory fashion and the interactions of treatment with subgroups were tested to identify differing treatment effects in subgroups with regard to the primary safety variable of non-CABG related major bleeding events. None of the interaction p-values in the ITT population met the predefined threshold value of $p<0.0028$. For intrinsic factors, only the age subgroups based on a cut-off at 65 years showed an interaction p-value of less than the unadjusted nominal $\alpha$ of 0.05 ($p=0.0318$). While bleeding rates were not significantly different in the subgroup of elderly patients aged ≥65 years (8.3% bivalirudin vs. 10.5% UFH plus GP IIb/IIIa; $p=0.1716$) the difference in major bleeding rates was statistically significant in favour of the bivalirudin arm in younger patients aged <65 years (3.0% vs. 6.9%; $p<0.0001$).

**Pharmacovigilance**

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

**Risk Management Plan (RMP)**

Bivalirudin risk management plan (RMP version 4.0) was first submitted by the MAH on 15/11/2007. An updated version of the RMP (version 5.0) has been submitted on 5/12/2008 as part of the submission of an extension of indication for Bivalirudin for its use as an anticoagulant in primary PCI in patients with ST elevation myocardial infarction (STEMI).

The RMP v5.0 submitted has been updated in the light of the results in HORIZONS-AMI and BIAMI studies, together with the post-marketing experience. The RMP follows the EMEA guidelines on risk management system for medicinal products for human use. According this guideline, safety concerns are classified as identified risks or potential risks. For each safety concern the following information is included: safety specification, pharmacovigilance plan, evaluation of the need for risk minimisation activities and, where appropriate, a risk minimisation plan. The Bivalirudin clinical database is large and includes patients with IHD across a broad spectrum of risk within the cardiovascular disease continuum. Its size allows the identification of AEs occurring with a frequency as low as 1 event per 10.000 patients.

HORIZONS-AMI study includes patients of a higher risk within the cardiovascular disease continuum as compared to previous studies (REPLACE-2, ACUITY). In this regard, the total incidence of AEs/SAEs reported in HORIZONS-AMI was higher than that in REPLACE-2 and ACUITY trials possible driven by the worst clinical profile of the patients included.
The general safety profile of bivalirudin is well characterized based in previous studies. **Identified risks** for Bivalirudin in the updated version of the RMP (v5.0) includes: Medication error, bleeding events and serious immunological disorders. **Potencial risks** for Bivalirudin included are: INR increase following co-administration of warfarin and Bivalirudin; Adverse events leading to cardiac arrest; Thrombocytopenia with Bivalirudin given concomitantly with GPI. All these safety concerns were in the previous version of the RMP. Neither additional pharmacovigilance activities nor additional risk minimization strategies are needed in the light of results in HORIZONS-AMI/BIAMI studies and post-marketing experience.
**Stent thrombosis (ST)** has been included in the RMP v5.0 as new potential safety concern in the light of results in HORIZONS-AMI study. Routine pharmacovigilance activities and routine risk minimisation activities are proposed by the MAH. The CHMP's main conclusions are summarized below:

***** No significant differences were observed in 30-days stent thrombosis between Bivalirudin and UFH+GPI arms (2.3% vs 1.9% respectively). Although this, patients on bivalirudin are at increased risk of acute ST (<24h) as compared to UFH+GPI (1.3% vs 0.2, $p=0.0002$). This increased risk has been observed in a setting of a randomized clinical trial with an adjudication of stent thrombosis events. In spite of this, it has been classified by the MAH as "potential risk" rather than "identified risk that requires further investigation". The MAH should provide a justification for this classification of the risk as "potential".

* The prognostic implications of acute stent thrombosis (<24 h) appear to be less severe than that in sub-acute stent thrombosis (24h-30 days) and mortality rates reported were of 7.4% and 34.7% for acute and sub-acute stent thrombosis respectively. This has been related to acute stent thrombosis occurring in closely monitored hospitalized patients, while sub-acute stent thrombosis occurs mostly after discharge. Given this, the MAH suggests that the risk is effectively minimized by intensive clinical observation and management post-PCI. In this regard, median hospital stay after PCI reported in the literature is 2 days (Silber S 2005, Lenzen MJ 2005). Besides, according figures in table 3.1.2.2.2 in HORIZONS-AMI study CSR, 28 out of 49 subacute ST (57.1%) happened within index-hospital. Thus, for a better characterisation of this safety concern, results on death rate by in-hospital/out-hospital setting should be provided regardless the timing it happened.

* Routine pharmacovigilance activities proposed by the MAH to monitor stent event thrombosis include: active follow-up of events; monthly review of reports and discussion of events in the PSUR. This proposal is adequate at this stage. Nevertheless, the MAH should keep on addressing this issue in all the clinical trials and observational studies to be performed and this should be specified in the RMP. This would be useful for a better characterization and quantification of this safety concern and, in general, of the early (first days) disadvantage in other outcomes observed in patients on Bivalirudin.

* Routine risk minimisation activities proposed by the MAH are changes in SPC including: dosing information; inclusion of the term "coronary stent thrombosis' in the ADR table of HORIZONS study and a warning in section 4.4 ("patients should be carefully monitored following primary PCI for signs and symptoms consistent with myocardial ischaemia". SPC changes proposed by the MAH to minimize the risk are perceived as insufficient. More detailed information and figures of the stent thrombosis findings in the HORIZONS-AMI study should be included in the SPC.

| Proposed pharmacovigilance activities (routine and additional) | Proposed risk management activities (routine and additional) |
|---|---|
| Routine pharmacovigilance in addition to:<br>• Expedited reporting of serious bleeding events (per regulatory requirements)<br>• Active monitoring and surveillance of bleeding events including the use of follow-up questionnaires to ensure high quality and complete information.<br>• Inclusion of discussion of bleeding reactions in the PSUR<br>• A quarterly analysis of appropriateness of product use in the EU<br>• Evaluation of any new risk factors for bleeding events on a monthly basis | Routine measures<br>Identified risks with respect to bleeding are considered well described in current labelling (see below), are responsive to aggressive surveillance and communication, and are unlikely to benefit from additional measures.<br><br>***Section 4.3:*** *Active bleeding or increased risk of bleeding because of haemostasis disorders and/or irreversible coagulation disorders.*<br><br>***Section 4.4:*** Haemorrhage: Patients must be observed carefully for symptoms and signs of bleeding during treatment particularly if bivalirudin is combined with another anticoagulant (see section 4.5). Although most bleeding associated with bivalirudin occurs at the site of arterial puncture in patients undergoing PCI, haemorrhage can occur at any site during therapy. Unexplained decreases in haematocrit, haemoglobin or blood pressure may indicate haemorrhage. Treatment should be stopped if bleeding is observed or suspected.<br><br>***Section 4.5:*** From the knowledge of their mechanism of action, combined use of anti-coagulant medicinal products (heparin, warfarin, thrombolytics or antiplatelet agents) can be expected to increase the risk of bleeding.<br><br>*In any case, when bivalirudin is combined with a platelet inhibitor or an anticoagulant drug, clinical and biological parameters of haemostasis should be regularly monitored.*<br><br>***Section 4.8:***** Tables 1, 2 and 3 summarise adverse rections from the HORIZONS, ACUITY and REPLACE-2 studies respectively. Many of these reactions are bleeding events.<br>Platelets, bleeding and clotting data for bivalirudin are summarised separately in this section (see below).<br>In the HORIZONS study both major and minor bleeding occurred commonly (≥1/100 and <1/10). The incidence of major and minor bleeding was significantly less in patients treated with bivalirudin versus patients treated with heparin plus a GPIIb/IIIa inhibitor. The incidence of major bleeding is shown in Table 8). Major bleeding occurred most frequently at the sheath puncture site. The most frequent event was a haematoma <5 cm at e puncture site (see Table 4).*<br><br>*Table 4: HORIZONS trial; 30-day bleeding site frequency data for the intent-to-treat population*<br><br>*In the ACUITY study minor bleeding occurred very commonly (≥ 1/10) and major bleeding occurred commonly (≥1/100 and <1/10). Both major and minor bleeds were significantly less frequent with bivalirudin alone than the heparin plus GPIIb/IIIa inhibitor and bivalirudin plus GPIIb/IIIa inhibitor groups (see Table 8). Similar reductions in bleeding were observed in patients who were switched to bivalirudin from heparin-based therapies (N = 2076).*<br><br>*Major bleeding occurred most frequently at the sheath puncture site (see Table 5). Other less frequently observed bleeding sites with greater than 0.1% (uncommon) bleeding included "other" puncture site, retroperitoneal, gastrointestinal, ear, nose or throat.*<br><br>*Table 5. ACUITY trial; 30-day bleeding site frequency data for the intent-to-treat population.*<br><br>*In the REPLACE-2 study, minor bleeding occurred very commonly (≥ 1/10) and major bleeding occurred commonly (≥1/100 and <1/10). Both minor and major bleeds were significantly less frequent with bivalirudin than the heparin plus GPIIb/IIIa inhibitor comparator group. The incidence of major bleeding is shown in Table 8. Major bleeding occurred most frequently at the sheath puncture site (see Table 6). Other less frequently observed bleeding sites with greater than 0.1% (uncommon) bleeding included "other" puncture site, retroperitoneal, gastrointestinal, ear, nose or throat.*<br><br>*Table 6. REPLACE-2: bleeding site frequency data (bivalirudin versus heparin + GPIIb/IIIa inhibitor).*<br><br>*Thrombocytopenia*<br><br>*In the HORIZONS study, thrombocytopenia was reported in 23 (1.4%) of bivalirudin-treated patients and in 67 (3.9%) of patients treated with heparin plus a GPIIb/IIIa inhibitor. All of these patients received concomitant acetylsalicylic acid, all but one received clopidogrel and 12 also received a GPIIb/IIIa inhibitor. In ACUITY thrombocytopenia was reported in 10 bivalirudin-treated patients (0.1%). The majority of these patients received concomitant acetylsalicylic acid and clopidogrel, and 6 out of the 10 patients also received a GPIIb/IIIa inhibitor. In REPLACE-2 Thrombocytopenia occurred in 20 bivalirudin-treated patients (0.7%). The majority of these patients received concomitant acetylsalicylic acid and clopidogrel, and 9 out of the 20 patients also received a GPIIb/IIIa inhibitor. In the HORIZONS study, 4 of the 23 patients who developed thrombocytopenia died. Mortality among the bivalirudin treated patients in the REPLACE-2 and ACUITY studies was nil.*<br><br>*Post-marketing experience*<br><br>*Adverse reactions that have been reported from extensive post-marketing experience and that have not been reported above are summarised by system organ class in Table 7.*<br><br>*Serious bleeding, including bleeding with a fatal outcome has been reported in post-marketing experience for bivalirudin.*<br><br>*Table 7. Post-marketing adverse reactions reported for bivalirudin (*includes intracranial haemorrhage and haematoma).<br><br>*Table 8. Major bleeding rates in clinical trials of bivalirudin 30 day endpoints for intent-to-treat populations .*<br><br>***Section 4.9:*** *In cases of overdose, treatment with bivalirudin should be immediately discontinued and the patient monitored closely for signs of bleeding.*<br><br>**Section 5.1:***Major bleeding rates from the HORIZONS are shown in Tables 9 & 10. Bleeding rates from the ACUITY study are provided in Table 13 and from REPLACE-2 in Table 14. |

***Discussion***

The CHMP agreed in September to convene a SAG-C in order to clarify the major outstanding issues of the procedure. The SAG-C meeting was held on 30th September 2009. The main pending issues pertained to the real causes of death across the whole HORIZON study to allow a proper ascertainment of the benefit/risk, including the impact of stent thrombosis and major bleeding (and subsequent management) on mortality rates and the implications of pre-treatment with heparin in terms of recommendations if any, for the Angiox prescribing information. Additionally, an assessment of the applicant's response to the other concerns (applicability of the data from Study HORIZON to a clinical situation where patients could be less intensively monitored, as it could be the case in clinical practice) was also discussed in the SAG-C meeting.

***Questions addressed at the SAG-C meeting***

***The applicant should provide more detailed information on the real causes of death across the whole study to allow a proper ascertainment of the benefit/risk.***

***The applicant should complete with actual data the table below (Annex LOQ). In addition, the Applicant should discuss the impact of early stent thrombosis seen in the bivalirudin arm and its subsequent management on the overall mortality seen in the HORIZON study.***
***The applicant should investigate mortality rates between treatment groups in patients who needed treatment cessation (BVR/UFH+GPIIb-IIIa/aspirin/clopidogrel) due to bleed and in those who did not require treatment cessation due to bleed, for the total 30-day study period and separately during and after hospitalisation, in order to ascertain if treatment withdrawal and subsequent rebound hypercoagulation, rather than the development of bleeding events (only 2 deaths were related to bleed), should have influenced the higher mortality rates in the UFH+GPIIb/IIIa group.***

The HORIZONS study was designed to reflect the current European trends in the management of STEMI patients undergoing PCI and compared bivalirudin to UFH with routine use of GP IIb/IIIa inhibitors.

There was a higher rate of early MACE (secondary to TVR) in the bivalirudin arm which was directly attributable to the occurrence of acute (<24 hours) stent thrombosis. Acute stent thrombosis did not impact mortality as only two patients died subsequently, one in each randomised group. In contrast, a total of 17 deaths occurred subsequent to subacute stent thrombosis, 3 in the bivalirudin arm and 14 in the UFH + GP IIb/IIIa arm. There was no statistically significant difference in the rates of overall stent thrombosis between treatment arms at 30 days (p=0.3257) or 1 year (p =0.7754).

The numerically higher rate of TVR observed in the bivalirudin arm was secondary to stent thrombosis events. In order to more fully understand the relationship between stent thrombosis, TVR, and death, the requested table has been completed (Appendix 1: Annex LOQ) and describes mortality patterns during index hospitalisation, after discharge through 30 days, and during the entire 30-day follow-up period.

During index hospitalisation, there was an increase in any stent thrombosis (2.2% versus 1.3% in the bivalirudin and UFH + GP IIb/IIIa arms, respectively) and a corresponding increase in ischaemic TVR (2.2% versus 1.4% in the bivalirudin and UFH arms, respectively) observed in patients treated with bivalirudin. Conversely, after discharge, there was an increase in any stent thrombosis occurring in the UFH + GP IIb/IIIa arm (0.6% versus 0.9% in the bivalirudin and UFH + GP IIb/IIIa arms, respectively). Patients with any stent thrombosis were more likely to undergo ischaemic TVR if treated with bivalirudin (83.7% [36/43] versus 61.8% [21/34]). This observation was directly associated with the timing of the stent thrombosis events. In patients experiencing any stent thrombosis within the 30 days, 81.3% (35/43) in the bivalirudin arm occurred during hospitalisation (with a median time of onset of 1 day) compared to 58.8% (20/34) in the UFH + GP IIb/IIIa arm (with a median time of onset of 7 days).

There was no difference in the 30-day rate of any stent thrombosis (2.7% versus 2.1% in the bivalirudin and UFH + GP IIb/IIIa arms, respectively). However, as a direct consequence of the timing of onset of stent thrombosis, there was a significant increase in mortality subsequent to stent thrombosis in patients treated with UFH + GP IIb/IIIa inhibitors (9.3% versus 44.1% in the bivalirudin and UFH + GP IIb/IIIa arms, respectively). Patients who had early stent thrombosis were more likely to be monitored, undergo TVR, and therefore survive than those experiencing later stent thromboses. Therefore, the timing of events is critical in understanding the reason for patient outcomes.

As tested in the control arm of the HORIZONS trial, the use of GP IIb/IIIa receptor blockade during PCI (in addition to dual antiplatelet therapy) has not been associated in clinical trials with a lower risk of stent thrombosis, but rather later onset of stent thrombosis [Assali et al, 2000; Rinaldi et al, 2008]. This exact pattern of events was reproduced in HORIZONS and the prognostic implications of the timing of stent thrombosis observed in the HORIZONS trial are consistent with those reported in the literature [van Werkum et al, 2009b].

In HORIZONS, bivalirudin patients experienced more stent thrombosis events early, with 50% occurring within 24 hours, while patients were most closely monitored. In these patients, the early onset and rapid recognition of symptoms, together with the rapid access to TVR, resulted in effective management. In patients administered UFH + GP IIb/IIIa inhibitors, 50% of the stent thrombosis events occurred after 7 days during periods of reduced patient monitoring, leading to a differential application of TVR between the randomised arms and subsequently higher mortality.

However, patients randomised to bivalirudin had better 30-day mortality, regardless of whether or not they had stent thrombosis or TVR (Table 1). Importantly, there was an approximate 1% difference in absolute mortality at 30 days in patients with no ischaemic TVR (1.9% versus 2.8% in the bivalirudin and UFH + GP IIb/IIIa arms, respectively; p=0.0827), consistent with the overall 30-day mortality results. Thus, the observed mortality benefit with bivalirudin was independent of the management of acute stent thrombosis with TVR. Treatment with bivalirudin improved mortality both in patients who did receive TVR (2.8% versus 18.2% in the bivalirudin and UFH + GP IIb/IIIa arms, respectively) and did not receive TVR (42.9% versus 91.7% in the bivalirudin and UFH + GP IIb/IIIa arms, respectively). The mechanisms for this observation are likely based on the beneficial effects of ischaemic preconditioning which may have preferentially protected patients with early stent thrombosis (predominantly in the bivalirudin arm) versus patients with later stent thrombosis (predominantly in the UFH + GP IIb/IIIa arm) [Hoole et al, 2009; Kukreja et al, 2009]. Ischaemic preconditioning occurs subsequent to any ischaemic myocardial injury and results in a biphasic pattern of myocardial protection. An early phase acts within minutes and lasts for several hours and a second window of protection occurs between 24 and 72 hours [Broadhead et al, 2004]. The difference in the median onset of stent thrombosis of 1 day versus 7 days may have bestowed a serendipitous advantage in the form of preconditioning on patients treated with bivalirudin.

Early stent thrombosis was appropriately managed with TVR. The successful use of TVR resulted in low mortality rates subsequent to acute stent thrombosis, as only two patients died, one in each randomised arm. Importantly, the observed mortality benefit with bivalirudin was not a result of the management of acute stent thrombosis with TVR, as clearly shown by directional mortality benefits in patients independent of stent thrombosis or the application of TVR.

***The applicant should investigate mortality rates between treatment groups in patients who needed treatment cessation (BVR/UFH+GPIIb-IIIa/aspirin/clopidogrel) due to bleed and in those who did not require treatment cessation due to bleed, for the total 30-day study period and separately during and after hospitalisation, in order to ascertain if treatment withdrawal and subsequent rebound hypercoagulation, rather than the development of bleeding events (only 2 deaths were related to bleed), should have influenced the higher mortality rates in the UFH+GPIIb/IIIa group.***

In HORIZONS, 251 patients experienced a major bleed within 30 days. Of the 93 deaths, 27 followed a major bleed, 10 followed a re-infarction, 9 followed ischaemic TVR, and 3 followed a stroke. According to the trial protocol, deaths were adjudicated as "related to bleeding" when patients literally haemorrhaged to death. In HORIZONS, only two deaths were causally adjudicated as "related to

bleeding." Bleeding may lead to a change in the subsequent management of patients which may consequently put the patient at a higher risk of future complications. One such example is the cessation of oral antiplatelet agents and also the discontinuation of antithrombotics [Bassand et al, 2007; Wang et al, 2008; Wiederkehr et al, 2009]. While this phenomenon has been reported in clinical practice, in the HORIZONS trial there was no overall difference between randomised groups with respect to compliance of antiplatelet therapies and most importantly there was no apparent association between major bleeding, mortality and discontinuation of antiplatelet therapies.

In patients treated with bivalirudin, there was no reduction in the median duration of bivalirudin infusion in patients with major bleeding (82.5 minutes) versus patients with no major bleeding (53.0 minutes). In patients treated with UFH + GP IIb/IIIa inhibitor, there was no difference in the median dose of heparin administered in patients with major bleeding (40.00 U/kg) when compared to patients with no major bleeding (42.95 U/kg). There was also no difference in the median duration of infusion of GP IIb/IIIa inhibitors in patients with major bleeding (12.08 hours) when compared to those without major bleeding (12.15 hours). In summary, there was no difference in the median duration of randomised therapy regardless of major bleeding complications.

During the HORIZONS study (hospitalisation period) there were 35 (2.2%) stent thrombosis in the bivalirudin arm versus 20 (1.3%) in the UFH+GPIIbIIIa inhibitor control group ($p = 0.0462$). Nevertheless, mortality rates in patients with stent thrombosis during hospitalisation were 11.4% in the bivalirudin group and 50% in the control group ($p = 0.0016$). Therefore, there was an imbalance in TVR techniques and subsequent in hospital mortality due to the temporal pattern of stent thrombosis.It has been seen in HORIZONS study that bivalirudin patients experienced more stent thrombosis events early, with 50% occurring within 24 hours, while patients were most closely monitored. In these patients, the early onset and rapid recognition of symptoms, together with the rapid access to TVR, resulted in effective management. In patients administered UFH + GP IIb/IIIa inhibitors, 50% of the stent thrombosis events occurred after 7 days during periods of reduced patient monitoring, leading to a differential application of TVR between the randomised arms and subsequently higher mortality.

The hypothesis of a ischaemic preconditioning (whereby prior sublethal ischemia induces a state of protection against subsequent prolonged ischemia-reperfusion injury) to support that the lower antithrombotic effect of bivalirudin resulting in higher rates of early stent thrombosis in the bivalirudin group provides a "paradoxical" protection in mortality is a weaker explanation than the objective data indicating a higher rate of TVR in patients with early stent thrombosis (most in the bivalirudin group) compared with those with subacute or late stent thrombosis (most in the UFH + GPIIbIIIa inhibitor group), which is considered by the CHMP to be the most important cause of the differential mortality rates observed during the HORIZON study.

The SAG acknowledged that, although there was a higher risk of acute stent thrombosis with bivalirudin, acute stent thrombosis is manageable. On the contrary, the higher rates of subacute stent thromboses with UFH are more difficult to be managed and probably associated with a higher mortality rates. The open nature of the HORIZONS study could have induced to investigators to take a higher level of awareness of acute ischaemic complications in patients on bivalirudin with a subsequent earlier management of these complications, leading to a higher rate of TVR in the bivalirudin group. However, the SAG agreed that regardless the cause for a lower mortality in the bivalirudin group, the fact is that mortality rates were reduced with bivalirudin at 30 days.

In conclusion, the CHMP is satisfied with the applicant response and therefore this issue could be considered as solved.

***According to the data provided, there appear to be significant differences in the MACE endpoint amongst patient in the Angiox arm who were pre-treated with heparin, compared to those who were not. This difference was not observed in the control group. The Applicant should discuss the implications of these findings in terms of recommendations if any, for pre-treatment with heparin. The MAH should provide the analysis of MACE and components at 30 days by pre-randomisation heparin use in the ITT population including the RR (95% CI) and p values.***

The HORIZONS trial did not demonstrate a statistical interaction between randomised therapy and pre-treatment with UFH in terms of MACE (p=0.1060). The view of the MAH is that this should be regarded as the most scientifically rigorous interpretation of this finding. The HORIZONS trial reflects the European practice of early initiation of adjunctive therapy. Published data supports this practice, specifically for clopidogrel, when given in addition to aspirin, oxygen, morphine and UFH. In view of this, and despite the lack of a statistical interaction, the revised SPC now reflects the need for early adjunctive therapy in the target patient population.

In patients treated with bivalirudin who received UFH pre-randomisation, there was an associated reduction in MACE driven by reductions in TVR at 30 days. Patients who received pre-randomisation heparin had lower rates of acute stent thrombosis regardless of treatment assignment. In this study, the administration of pre-randomisation heparin appears to have been associated with numerically improved acute stent thrombosis events in both the bivalirudin and the UFH + GP IIb/IIIa inhibitor-treated patients.

Definitive data demonstrating the benefits of early heparin administration on ischaemic outcomes are not available. Typically, intravenous UFH is given during the procedure to patients undergoing primary PCI to prevent acute vessel closure due to thrombosis. There is no published evidence that prolonged use of heparin will prevent ischaemic complications, but an added risk of increased bleeding complications has been reported [Tolleson et al, 2003].

Based on the observation of increased bleeding complications in patients switching between UFH and LMWH heparin-based regimens, this practice is strongly discouraged and patients are recommended to remain on the original anticoagulation started at the time of first medical contact [Mahaffey and Ferguson, 2005; Drouet et al, 2009]. The prolonged half life of both drugs, further compounded by the unpredictable dose response effect of UFH, may underpin this finding.

Published evidence supports early administration of anti-thrombotic therapy. In the HORIZONS study almost all patients (96.7%) received either a 300 mg or 600 mg loading dose of clopidogrel. A 600 mg loading dose of clopidogrel was used almost twice as frequently as 300 mg in accordance with the current ESC guidelines [Van de Werf et al, 2008]. 30-day MACE events in both treatment arms were numerically improved in patients receiving 600 mg clopidogrel.

It is likely that the relationship between early initiation of UFH and the observation of decreased acute stent thrombosis is one of association and not causation. Unlike the literature regarding UFH, studies with clopidogrel have consistently demonstrated the clinical benefits of its early administration. The early co-administration of UFH along with other therapeutic agents, such as aspirin and clopidogrel, is the standard of care in these high-risk patients. However, the early administration of clopidogrel, but not heparin, has been shown to improve outcomes in patients with STEMI undergoing primary PCI [Vlaar et al, 2008; Fefer et al, 2009]. In a recent meta-analysis of 8,429 patients, initial infarct related artery patency was higher in patients who received pre-treatment with clopidogrel (34.3%; 95% CI 32.9 - 35.8) compared with those in which patients did not receive clopidogrel before initial coronary angiography (25.8%; 95% CI 24.5-27.1). In multivariate-weighted logistic regression analysis, pre-treatment with clopidogrel was an independent predictor of early reperfusion (OR, 1.51; 95% CI 1.31-1.74; $p<0.0001$), and improved clinical outcomes including mortality [Vlaar et al, 2008]. In another recent study the benefits of pre-loading as well as the advantages of 600 mg versus 300 mg of clopidogrel loading were highlighted with a significant reduction in 30-day stent thrombosis (2% versus 7%; $p = 0.04$) in favour of patients pre-loaded with 600 mg clopidogrel versus alternative strategies [Fefer et al, 2009].

The pre-specified subgroup analysis comparing MACE in patients with and without pre-randomisation UFH showed no formal statistical interaction. The lower incidence of MACE events observed in patients pre-treated with UFH was driven by lower rates of TVR subsequent to acute stent thrombosis. This observation was noted in both treatment arms. Published clinical data have not demonstrated a benefit for UFH in reducing ischaemic events and demonstrate an association with increased bleeding. In HORIZONS, the observation of numerically reduced acute stent thrombosis in bivalirudin patients pre-treated with UFH may represent an association with the therapeutic benefits of early concomitant

administration of other potent antithrombotic medications such as clopidogrel that have been shown to improve outcomes in patients with STEMI undergoing primary PCI. In order to inform physicians of the optimal pharmacotherapeutic regimen, the MAH is amending Section 4.2 of the SPC.

***The applicant should try to identify any specific patient characteristics which could have predisposed to acute stent thrombosis in the control arm.***

Stent thrombosis may occur at any time after the implantation of a coronary stent. It is caused by thrombus formation within the lumen of a deployed stent and manifests clinically as signs and symptoms of myocardial ischaemia. There are many factors that may predispose patients to stent thrombosis including genetic factors such as CYP 2C19 polymorphism [Sibbing et al, 2009] as well as angiographic and procedural factors such as primary PCI for STEMI [Urban et al, 2006], presence of angiographic thrombus [Moussa et al, 1997, Fokkema et al, 2009], the use of a coil or self-expanding stents [Lansky et al, 2000], greater stent length [Cutlip et al, 2007; Iakovou et al, 2005], renal failure and discontinuation of antiplatelet therapy [Ong et al, 2005].

These individual reports are hampered by small sample size, retrospective character of study design, and variation in the definition of stent thrombosis. However, the relevance of these factors is supported by recent data from a large European registry of over 21,000 patients. In this registry, the strongest individual predictors of stent thrombosis include discontinuation of clopidogrel, undersizing of the coronary stent, presence of intermediate coronary artery disease proximal to the culprit lesion, and concomitant malignant disease [van Werkum et al, 2009]. In this analysis, risk factors for stent thrombosis also varied across the different indications for PCI (stable angina versus ACS) and differed for the different categories of stent thrombosis (early versus late stent thrombosis). The cumulative incidence of stent thrombosis was highest in STEMI patients undergoing PCI; these events were more frequently "acute" stent thrombosis.

The use of GP IIb/IIIa receptor blockade during PCI (in addition to clopidogrel and aspirin) has not been associated with a lower risk of stent thrombosis, but rather a later onset of stent thrombosis [Rinaldi et al, 2008, Assali et al, 2000]. This later onset "subacute" stent thrombosis was reproduced in HORIZONS, where no difference in overall 30-day stent thrombosis (2.7% bivalirudin versus 2.1% UFH plus GP IIb/IIIa, p=0.3257) but a numerical increase in sub-acute stent thrombosis (1.2% bivalirudin versus 1.9% UFH plus GP IIb/IIIa, p=0.1416) was observed. This later onset of subacute stent thrombosis was associated with increased subsequent mortality (17 subsequent deaths) when compared to bivalirudin (3 subsequent deaths). This finding of increased mortality associated with subacute stent thrombosis has also been identified in other studies [van Werkum et al, 2009].

In addition to angiographic and patient characteristics, platelet activation is reported to play a pivotal role in mediating stent thrombosis as is highlighted by the association with genetic factors such as platelet loss of function CYP 2C19 polymorphism [Sibbing et al, 2009] and the role of effective platelet inhibition seen in other contemporary trials [Wiviott et al, 2008]. The importance of platelet inhibition was further demonstrated in HORIZONS, where patients who did not receive clopidogrel (regardless of randomised therapy) were more likely to experience acute stent thrombosis (2.8%) than patients who did receive clopidogrel, 300 mg (0.7%) or 600 mg (0.8%). There was a reduction stent thrombosis from 24 hours to 30 days in patients receiving 600 mg (1.2%) versus 300 mg (2.4%) however; the administration of 600 mg versus 300 mg of clopidogrel did not appear to affect acute stent thrombosis events. It should be noted that the MAH has proposed a label change in Section 4.2 of the SPC to the effect that in patients with STEMI undergoing primary PCI, early therapy should include a 600 mg loading dose of clopidogrel.

The use of drug eluting stents has previously been associated with increased risk of early stent thrombosis [van Werkum et al, 2009]. Although not significant, this finding was replicated in the HORIZONS trial which demonstrated that patients who received a drug eluting stent were more likely to experience an acute stent thrombosis. Patients who received a bare metal stent were more likely to experience a subacute stent thrombosis.

In HORIZONS, patients who received pre-randomisation heparin had numerically lower rates of acute stent thrombosis regardless of treatment assignment. This observation is contrary to randomised controlled trial data which failed to demonstrate any ischaemic benefit associated with early administration of high dose heparin [Liem et al, 2000]. Collectively, these data suggest it is more likely that the pre-treatment with heparin is a surrogate of earlier initiation of other concomitant antithrombotic therapies, coinciding with the early concomitant administration of clopidogrel that has repeatedly been shown to improve both ischaemic outcomes and stent thrombosis in patients with STEMI undergoing primary PCI [Vlaar et al, 2008, Fefer et al, 2009].

Post-hoc analyses from HORIZONS identified patient and procedural characteristics associated with the occurrence of acute stent thrombosis, including advanced age, lesion characteristics (aneurysm, ulceration) and poor flow. The aetiology of acute stent thrombosis is multi-factorial and cannot be fully resolved based on this dataset.

To further characterise the finding of acute stent thrombosis, the size and scope of the ongoing Drug Utilisation Study will be increased to include STEMI patients to assess outcomes in European patients receiving Angiox. Further, to enhance the awareness of acute stent thrombosis and the need for vigilance in patients undergoing primary PCI, the MAH has proposed updates to Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects) of the SPC.

This issue is considered resolved by the CHMP.

***Considering the newer trends for early discharge after PCI, the advisability of such an approach with Angiox is highly questioned. The MAH should further discuss the extrapolability of the data from Study HORIZON to a clinical situation where patients could be less intensively monitored, as it could be the case in clinical practice. The MAH should discuss specific measures to ensure proper monitoring and the availability of TVR during the first 24 hours from PCI.***

The risk of death following stent thrombosis may be effectively minimised by careful monitoring and rapid access to a catheter laboratory for TVR. Based on current European guidelines, all patients should be carefully monitored following primary PCI, including a recommendation of 24 hours of ECG monitoring. The MAH has provided data on the transfer between institutions in the HORIZONS study and length of stay. A total of 61% of patients were initially admitted to a hospital with PCI facilities (treatment hospital) and 39% were initially admitted to a referring hospital and then transferred to a hospital with PCI facilities. 18% of patients were transferred back to the referring hospital and only 2.7% were transferred back within 48 h. The remaining 82% of patients were discharged to home. Length of stay in the HORIZONS study was 6 days, which is in the usual range for PPCI (4 to 8 days).

This issue is considered resolved by the CHMP.

***The MAH has to provide a justification on the SPC recommendation for a post-procedural infusion. The Applicant should submit information about the occurrence of acute stent thrombosis in the 6.0% (105/1749) of patients who received a post-procedural infusion of bivalirudin as well as the rates of bleeding events and deaths in patients receiving post-procedural infusion compared with rates of events in patients not receiving post-procedural infusion.***

The MAH proposed to include the details of post-PCI infusion dosing as reflected in the HORIZONS protocol. In an emergent setting, various patients and procedural factors may encourage a clinician to continue anticoagulation for a brief period of time after PCI. Mechanistic data suggest that bivalirudin, when continued beyond the end of PCI, may be beneficial and historical clinical data confirm that this practice does not adversely affect the benefit:risk profile of bivalirudin. Previous pivotal studies of bivalirudin, including REPLACE-2 and ACUITY, have included this dosing option for clinicians.

The applicant has proposed a recommendation in section 4.2 of the SPC for a post-procedural infusion of 0.25 mg/kg/h as clinically necessary for primary PCI. Only 105 patients in the HORIZONS study

received this post-procedural infusion and there was a numerically higher rate of stent thrombosis and bleeding in patients receiving this post-procedural infusion compared with no post-procedural infusion. Nevertheless, the decision to apply a post-procedural infusion was left to the investigators' criteria, "as clinically necessary". Therefore, clinical status of patients receiving post-procedural infusion might not be comparable to those not receiving the post-procedural infusion and no definitive conclusions may be tempted in this regard based solely on the data from the HORIZONS study. The recommendation of a post-procedural infusion of 0.25 mg/kg/h as clinically necessary is already included in the Angiox SPC for ACS and PCI, based on the results from the REPLACE-2 and ACUITY studies. Therefore, to be consistent with current SPC, the MAH's proposal is acceptable by the CHMP.

***Risk Minimisation plan- The MAH should extend the duration and sample size of the current drug utilisation study to ensure that patients with STEMI undergoing primary PCI to further characterise the risk of acute stent thrombosis. An updated protocol for the study should be provided to reflect the extensions.***

The MAH has committed to expand the duration and sample size of the drug utilisation study to include patients in the new indication. An updated draft protocol is provided. The applicant has provided an updated protocol for the drug utilization study. The sample size is now proposed to be approximately 2000 patients and the study duration has been extended to end Q1-2 2011 in order to include patients with STEMI undergoing primary PCI. The updated protocol is satisfactory however the current status and milestones for the study are unclear as the study protocol states the anticipated study start is Q2 2009 whereas section 2.6 of the RMP does not contain milestones. The applicant should clarify the current status of the study and update the RMP with the study timelines. The CHMP has considered this issue solved subject the clarification of current status and milestones.

***The difference between doses of clopidogrel 300mg and 600mg is significant as the events were nearly double in patients receiving clopidogrel 300mg compared to those receiving clopidogrel 600mg. The MAH must include a statement the effect that clopidogrel 600mg should be the preferred dose in section 4.2.***

The MAH accepted the proposal to include wording in section 4.2 of the SPC.

***In addition, in this specific indication, a specific paragraph on concomitant treatments gathering information on pre-treatment by heparin, use of both aspirin and clopidogrel, use with GPIIb/IIIa inhibitors should be created to replace the current various mentions on this topic.***

The applicant has agreed to include a statement regarding pre-procedure heparin in the SPC.

***The following paragraph, currently mentioned in the SPC, has been omitted:***

> ***In patients with moderate renal impairment included in a pivotal phase III PCI study (REPLACE-2) ACT values assessed 5 minutes after bivalirudin bolus averaged 366 +/- 89 seconds with no dose adjustment. At the end of the PCI procedure, the ACT values averaged 355 +/- 81 seconds in these patients.***

A renewal application for Angiox was submitted in January 2009 and has subsequently been approved. During the renewal process the QRD group of the EMEA conducted a review of the SPC and commented that the paragraph regarding ACT levels in patients with moderate renal impairment was not clear and could be interpreted to mean that no dose reduction in Angiox is necessary. This was thought to conflict with a previous paragraph in the SPC where it is recommended that the infusion rate of Angiox should be reduced to 1.4 mg/kg/hour in patients with moderate renal impairment. In view of the fact that information regarding ACT values post Angiox dosing is already provided in the SPC (under adult dosing).. The CHMP is of the opinion that this point is resolved.

***The MAH must include a warning in the SPC sections 4.2, 4.4 and 4.8—regarding acute stent thrombosis, and the differences between heparin pretreated group and untreated group.***

The HORIZONS trial did not demonstrate a statistical interaction between randomised therapy and pre-treatment with UFH in terms of MACE (p=0.1060). The view of the MAH is that this should be regarded as the most scientifically rigorous interpretation of this finding.

The relationship between early initiation of UFH and the observation of decreased acute stent thrombosis may be one of association and not causation. Unlike the literature regarding UFH, studies with clopidogrel have consistently demonstrated the clinical benefits of its early administration. Angiox should be used in the context of current European practice guidelines, including a recommendation that in addition to aspirin, standard pre-hospital adjunctive therapy should include a 600 mg loading dose of clopidogrel and may include the early administration of UFH.

The MAH does accept the need for an explicit warning in section 4.4 of the SPC. With respect to Sections 4.2 and 4.8, the MAH agrees that appropriate labelling is needed to inform physicians and allow the early initiation of antithrombotic therapies.

The labeling strategy proposed by the MAH is therefore based upon the following:

- Informing physicians of the optimal pharmacotherapeutic regimen for patients with STEMI undergoing primary PCI, including the early administration of clopidogrel and UFH (Section 4.2).
- Warning physicians about the signs and symptoms of acute stent thrombosis and its subsequent management (Section 4.4).
- Describing the incidence of stent thrombosis and the relative significance of acute versus late stent thrombosis and how it impacts mortality in the HORIZONS trial (Section 4.8).

The CHMP accepts this justification and considers the point resolved.

***Section 4.4 it is necessary to add a paragraph on acute stent thrombosis.***

The MAH has agreed to its inclusion and the CHMP considers this point resolved.

***Section 4.8 (undesirable effects). The following issues should be clarified by the MAH.***

- For some of the ADR included in the ADR tables (tables 1-3 new SPC) there is a table note stating that "the reaction has also been seen in post-marketing exposure". The frequencies of these ADRs have been properly quantified in the different clinical studies. According to this, the table note information does not provide additional information of interest, specially taking into account that it is likely that all others ADRs in the table had been observed in the post-marketing experience as well. The MAH should justify the reason for this or delete the table note.
- Information in Post-marketing experience: It is not clear the criteria used by the MAH to include the information in this section. Most of the adverse events included have valid estimations of their frequency from clinical trials. Consequently, they have been included in the corresponding cell of the ADR tables according the frequency observed in the different studies. Adverse events to be included in this section are those identified in the post-marketing experience with no proper estimation of its frequency in epidemiological studies and with, at least, a reasonable suspicion to be related with the drug (see European guidelines on SmPC, October 2005).
- In section 4.8, although figures of acute stent thrombosis by treatment arm are provided, the statistically significance observed is not mentioned. Conversely, the information about the lack of statistically significance at 30 days and 1 year is included in this section.

Concerning the ADRs tables and the information in the post-marketing exposure section, the MAH has deleted the footnote under tables 1, 2 and 3 and deleted the post-marketing exposure section. This is acceptable by the CHMP. Regarding the acute stent thrombosis figures provided, as requested, the new version of the SPC provided specifically mention the statistically significance disadvantage observed in patients on Bivalirudin in the first 24 hours and this is considered acceptable by the CHMP.

***Section 5.1 the description of the HORIZONS trial, it is mentioned that all patients received aspirin and clopidogrel. It should be added that 65% of subjects had been pre-treated with heparin.***

This section should not contain information that would not be well understood by physicians. For further clarity, some amendments should be done*:*

- Tables should be simplified. It is notably not necessary to mention the column Difference (95%CI). Relative risk and p-value columns are more than sufficient.
- Results should not be presented with both ITT and per protocol populations, since they are similar.
- It is not necessary to provide the definition of minor bleedings in REPLACE-2, ACUITY and HORIZONS studies since results for minor bleedings are not provided in section 5.1 of the SPC.

The MAH proposed to include the 1-year long-term follow-up data in this section. It should also be noted that the MAH has also been requested to update all 30-day HORIZONS data previously presented in the SPC with the 1-year trial database. The applicant has amended the SPC accordingly and agreed to include a text about pre-procedure heparin. This point is considered resolved by the CHMP.

The actions taken by the MAH to address the acute stent thrombosis issue are the following:

- re-classification of this risk as "identified risk that requires further investigation".

- routine risk management activities by communicating this risk in sections 4.2 (Posology and method of administration) 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects).

- Further evaluation of this risk in all clinical trials and observational studies to be performed with Bivalirudin.

All these actions are perceived by the CHMP as acceptable with the current evidence available. Nevertheless, results of HORIZONs showed that differences in MACE where higher in patients not pre-treated with heparin. This has a potential impact given that 65% of patients randomized were pre-treated with heparin.

The RMP has been updated with this information and proposed amendments to the SPC regarding pre-heparin (and clopidogrel) use. An updated version of the RMP (version 8) has been provided with these responses. The CHMP, having considered the data submitted, was the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product
- no additional risk minimisation activities were required beyond those included in the product information.

Following the overall assessment of the efficacy and safety data provided, the CHMP concluded that the benefit/risk ratio of Angiox is positive and agreed on the following final wording of the indication in section 4.1 of the SPC:

*"Angiox is indicated for patients undergoing percutaneous coronary intervention (PCI),* ***including patients with ST elevation myocardial infarction (STEMI) undergoing primary PCI****"*.

All the proposed consequential changes to sections 4.1, 4.2, 4.4, 4.8, 4.9 and 5.1 of the SPC and the package leaflet can be agreed.

Further, the MAH has taken the opportunity to update the contact details of the local representative for Greece, Spain, Portugal and France in the package leaflet, which is acceptable.
In addition, the MAH has updated annex IIB to reflect the latest RMP version (version 8) agreed with CHMP.

## II. CONCLUSION

On 22 October 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.